For The United States Patent and Trademark Office

Applicants:	Heil et al.
Application no.:	09/757,688
U.S. Filing Date:	11 January 2001
Title:	Drospirenone for Hormone Replacement Therapy
Examiner:	Laksmi S Channavajjala
Art unit:	1615

DECLARATION OF DR. Jörg ELLIESEN UNDER 37 C.F.R. §1.132

I, Jörg Elliesen of Berlin, Germany, one of the named inventors of the patent US 5,922,349 do state and declare as follows:

1. I believe that I am a person of ordinary skill in the art to which the above-captioned application pertains. Please find attached to this declaration my CurriculumVitae.

2. I am an employee of Schering Aktiengesellschaft, the assignee of the above-captioned application.

3. I have read and undcrstood the pending claims in the application in question as well as the Office Action related thereto, dated 24 October 2001, in which US 5,922,349 was first cited against the application in question. I have also read and understood the communication, dated 28 May 2002, which was filed in response to this Office Action. I have also read and understood the Office Action, dated 26 June 2002, in which the corresponding PCT application to US 5,922,349 is cited (WO 97/11680), I have the following comments:

4. US 5,922,349 and WO 97/11680 discuss pharmaceutical compositions comprising an estrogen and a progestin. Such compositions are of importance for HRT (hormone

replacement therapy) and for contraception. The compositions are provided in forms wherein it may be desirable to adjust the effective dose on an individual basis.

5. For the invention of US 5,922,349 and WO 97/11680, it was disclosed that the progestins applicable for use in the questioned device relate to natural as well as synthetic progestins which are known to give a clinical relevant response. Specifically mentioned were the synthetic progestins, norethisterone and its ester; norgestrel; levo-norgestrel; chlormadinone acetate; cyproterone acetate; desogestrel; 3-ketodesogestrel; drospirenone; norgestimate or gestodene. The natural hormone, progesterone, was also specifically mentioned, but natural occurring progesterone has rarely been used in clinical practice because of rapid hepatic metabolism and poor bioavailability (see the attached Appendix A, item 3, for example). At the time the invention was made it was generally known that synthetic progestins could be used in oral contraceptive preparations and to treat menopausal symptoms. However, progesterone had not been used because of the above-mentioned problems.

6. The prevailing knowledge in the art, both at the time of the invention and now, was/is that, for oral administration, progesterone had to be formulated in a special manner in order to achieve a clinically relevant response; see Appendix A, items 1-5. For example, it was known that the bioavailability of progesterone could be improved by suspending it in a fatty acid, reducing the particle size of progesterone, or by combining the techniques of reducing the particle size and suspending in fatty acids (see Appendix A, items 1 to 3 and 5). However, even after micronization of progesterone, the absolute bioavailability upon oral administration is only in the order of 6-8% (see the Lignieres article cited in the current Office Action, at page 43, column 1). Therefore, rather high doses of micronized progesterone are needed in order to achieve a clinical relevant response such as between 100 and 300 mg.

7. I believe that the phrase "micronized progesterone" has been a standard phrase in the art. It was the clear understanding in the art that progesterone needed to be provided in micronized (or other special) form in order to be clinically relevant. Natural progesterone not specially formulated was known to have no clinical relevance.

8. Thus, since it was known in the art that progesterone needed to be provided in micronized form, we indicated this in our patent application (WO 97/11680) by preceding the word "progesterone" by the term "micronized" so as to use the standard phrase in the art.

9. Accordingly, it was not our intention to mention that other progestins should be applied in micronized form.

10. I acknowledge that one who is not of ordinary skill in the art to which the invention pertains reading the WO 97/11680 disclosure at page 15, lines 8-18, or the US 5,922,349 disclosure at column 10, lines 16-28, could possibly have the impression that all the progestins mentioned are indicated to be in micronized form. However, I firmly believe that a person of ordinary skill in the art, who would know of the particular poor bioavailability of progesterone and of the standard phrase "micronized progesterone," would understand that that the word "micronized" was only meant to apply to progesterone and not the synthetic progestins. I would like to further note that it was our intention in writing the WO 97/11680 - US 5,922,349 disclosure only to mention that progesterone is in micronized form and not to imply that the other progestins should also be applied in micronized form.

11. Other parts of our disclosure are consistent with the progesterone and not the other progestins being in micronized form. After the listing of the progestins on page 15 of WO 97/11680, there is a listing of 4 preferred synthetic progestins, including drospirenone but not including progesterone. The term "micronized" does not appear in this listing. If the "micronized" term applied to all the progestins in the initial list, it would be inconsistent to not include it in the preferred list. Also, claim 12 of WO 97/11680 recites 3 synthetic progestins but does not recite that they are micronized. Finally, the synthetic progestin used in the Examples 1-3 is a synthetic progestin, not progesterone, and is not micronized. These parts of the disclosure are consistent with the "micronized" term pertaining only to progesterone and not drospirenone or other synthetic progestins.

12. In summary:

- it was known that natural progesterone did not give a clinically relevant response because of poor bioavailability and that progesterone needed to being provided in micronized form (or some other special form) to give a clinical relevant response;
- it was known that synthetic progestins, which are not metabolised so extensively in vivo as natural progesterone, resulted in a clinically relevant response upon being administered orally;
- thus, one of ordinary skill in the art would not have read the disclosure of US 5,922,349 or WO 97/11680 as disclosing the use of drospirenone in micronized form.

13. I further declare that all statements made herein of our knowledge are true, and further that the statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issued thereon.

Dated: 10.03.2003 Signature: J. Elliesen

Jörg Elliesen

Appendix A

Examples, wherein it is stated that progesterone, but not synthetic progestins need to be formulated properly, for example by micronization, in order to achieve a clinical relevant response:

1. Kincl F. A. et al. Increasing oral bioavailability of progesterone by formulation. J, Steroid Biochem, vol. 9, pp 83-84, 1978.

2. Whitehead M. I. Absorption and metabolism of oral progesterone. Br. Med. Journal, 22 March, pp 825-827, 1980.

3. Maxson and Hargrove. Bioavailability of oral micronized progesterone. Fertility and Sterility, vol 44, No 5, pp 622-626, 1985.

4. Chakmakjian and Zachariah. Bioavailability of progesterone with different modes of administration. Journal of reproductive medicine, vol 32, No 6, pp 443-448, 1987.

5. Hargrove J. T. et al. Absorption of oral progesterone is influenced by vehicle and particle size. A. J Obstet Gynecol, p 948-951, 1989.

CURRICULUM VITAE

Name:	Dr. med. Jörg Elliesen
Born:	July 7, 1959
Nationality:	German

Education and Qualifications

1969-1978	Secondary education (Droste-Hülshoff Gymnasium, Freiburg)
1978	Secondary school completion examination (Abitur)
1979-1985	Medical School, Free University of Berlin
1985	Approbation as physician
1993	Doctoral thesis (MD), Free University of Berlin

Employments

1986	Internship in internal medicine (Rudolph-Virchow Krankenhaus)
1987	Clinical Research and Development (Hormone Therapy), Schering AG Berlin
1996-1999	Medical & Scientific Affairs, Schering AG, Expert Position for Clinical Research
2000-2001	Clinical Development Andrology Jenapharm GmbH & Co. KG, Jena
2001-present	Corporate Clinical Development – Male FC/HT Schering AG, Berlin

adsorption efficacy of the vehicle employed) are ethinyl estradiol and estradiol and their esters, e.g., acetate, valerate, benzoate, succinate and undecylate (5-15 mcg/day), mestranol (25-25 mcg/day), estriol, estriol succinate, polyestriol phosphate, estrone, estrone sulfate and conjugated estrogens (5-15 mcg/day). Of these, ethinyl estradiol, 17ß-estradiol, conjugated estrogens and estrone ane especially ethinyl estradiol and 17ß-estradiol are preferred.

Examples of progestogen which can be employed in this invention (dosages shown are oral; transdermal dosages will vary therefrom in accordance with the adsorption efficacy of the vehicle employed) are micronized progesterone (15-50 mg/day), norethindrone and esters, e.g., acetate, thereof (0.1-0.75 mg/day), norethynodrel (0.3-0.6 mg/day); ethynodiol diacetate (0.3-0.75 mg/day), norgestrel (0.75-0.2 mg), levonorgestrel (0.03-0.1 mg/day), chlormadinone acetate, cyproterone, cytoproterone acetate, desogestrel, drospirorenone, norethindrone, dinorgestrel, norgestimate, levo-norgestrel, or gestodene (Schering AG, Berlin; U.S. Patent 4,081,537) (equivalent to 0.03-0.15 mg levo-norgestrel). Of these, gestodene, levo-norgestrel, 3-ketodesogetrel, desogestrel, 3-ketodesogetrel, drosprirenone and especially gestodene, levo-norgestrel and 3-ketodesogetrel are preferred.

The pharmaceutical compositions of this invention contain, for example, approximately from 0.2 to 20 mg of 17β-estradiol or approximately from 0.5 to 60 mg of norethisterone-17-acetate, or a biologically equivalent amount of another estrogen or gestagen, respectively. Preferred dosage forms contain approximately from 5.0 to 30 mg of norethisterone-17-acetate. These amounts are sufficient to ensure the release and absorption of minimum daily therapeutic amounts approximately equal to 0.05 mg of 17β-estradiol and approximately 0.2 mg of norethisterone-17-acetate, even when the hormones are applied only once every several days and the area of application is covered by an adhesive bandage.